II. REMARKS

Claims 1 to 21 are pending.

It is noted in the Office Action that claims 1 to 5 are allowed, and that claims 11 to 13 and 15 are objected to as depending from a rejected base claim.

A. Regarding the Amendments

A substitute Sequence Listing is submitted herewith. The substitute Sequence Listing merely lists the sequences set forth in Table 1 (page 70) of the application as originally filed. As such, the substitute Sequence Listing does not add new matter and, therefore, entry of the Sequence Listing is respectfully requested.

Table 1 (page 70) has been amended to insert Sequence Identifiers. A replacement page 70, in which the newly added SEQ ID NOS: are underlined (indicating addition), is attached to this Amendment (Appendix A). It is noted that underlining of specific nucleotides in Table 1 was present in the Table as originally filed, and is not indicative of newly added material. Since the amendment to Table 1 merely addresses a formality by adding Sequence Identifiers, entry of the replacement page 70 is respectfully requested.

Claims 9 and 18 have been amended to clarify that the claimed host cell is an "isolated" host cell. The amendment is supported, for example, at page 37, lines 12-15, which discloses that a vector can be used to introduce a nucleic acid molecule of the invention into a cell *ex vivo*, i.e., isolated from an organism. As such, the amendment does not add new matter.

Claims 20 and 21 have been amended to clarify that a "polynucleotide complementary to" a substantially pure oligonucleotide as recited is encompassed with the claimed subject matter, and to further clarify that such a complementary polynucleotide "comprises at least ten nucleotides ". The amendment is supported, for example, at page 4, line 30, to page 5, line 6, and, therefore, does not add new matter.

Claim 20 also has been amended to correct a typographical error, wherein the term "polynucleotide" inadvertently was used instead of the term "oligonucleotide". The amendment is supported by the language of claim 20, which provides the requisite antecedent basis for "said oligonucleotide." In addition, claim 20 has been amended to clarify that the claimed oligonucleotides hybridize specifically to the 5' and 3' nucleotide sequences "of SEQ ID NO:1", as defined. The amendment is supported, for example, at page 38, lines 8-12, and, therefore, does not add new matter.

Claim 21 also has been amended to recite that nucleotides 2412 to 2414 of SEQ ID NO:1 are operatively linked "and contiguous to" nucleotides 3768 to 3770 of SEQ ID NO:1, thus clarifying that the sequences are directly adjacent to each other. The amendment is supported, for example, at page 5, lines 12 to 18; and page 39, lines 4-10 (see, also, Figure 5B, uppermost construct, showing exon 1, which ends with nucleotides 2412 to 2414, directly linked to exon 3, which begins with nucleotides 376 to 3770). As such, the amendment does not add new matter.

B. Regarding the Sequence Rules

The specification is objected to as not complying with 37 C.F.R. § 1.821 et seq. for containing sequences that are not listed in the Sequence Listing or identified by a Sequence Identifier. A Substitute Sequence Listing, including paper copy and computer readable form, is submitted herewith containing a full listing of the sequences as disclosed in the subject application as originally filed. In addition, an amended page 70 is submitted herewith containing the Sequence Identifiers for the disclosed sequences. Accordingly, it is respectfully requested that this objection to the specification be withdrawn.

C. Regarding the Declaration

The Declaration is objected to as allegedly being defective for containing alterations that are not initialed and dated. Applicants have submitted herewith a new Declaration. Accordingly, it is respectfully requested that this objection be withdrawn.

D. Rejections under 35 U.S.C. § 112

The rejection of claims 29 under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite is respectfully traversed.

It is noted in the Office Action that the term "said polynucleotide" lacks antecedent basis. Claim 20 has been amended to correctly refer to "said oligonucleotide", for which antecedent basis is provided. Accordingly, it is respectfully requested that the rejection of claim 20 under 35 U.S.C. § 112, second paragraph, be removed.

The objection to the specification and corresponding rejection of claims 6 to 9 and 16 to 18 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

It is alleged in the Office Action that the claimed vectors and host cells are not enabled because the specification contemplates the use of such vectors for gene therapy, but the specification is not enabling for gene therapy. The rejection is supported by reference to the unpredictability of gene therapy methods as of the priority date of the subject application (November 1999), including, for example, the failure of the specification to teach methods for overcoming problems associated with *in vivo* delivery and expression of the claimed nucleic acids or viral vectors containing the nucleic acids.

Applicants point out, however, that the claims are directed to compositions, not to methods, and particularly not to methods of gene therapy. While it is true that the vectors of the invention can be used for gene therapy, there is no requirement in the claims that such vectors have any particular therapeutic benefit or, therefore, any requirement regarding delivery and/or expression. It is submitted that any *in vivo* use for the vectors should be

sufficient to meet the enablement requirement for the claimed compositions. In this respect, it is disclosed in the specification that the claimed vectors can be used, for example, to introduce an Mcl-1 regulatory element into cells *in vivo* for the purpose of identifying genes that can be activated by integration of the regulatory element into the genome (see, e.g., page 45, line 19, to page 46, line 16), or for expressing an operatively linked heterologous nucleic acid molecule in cells in which the Mcl-1 regulatory element has regulatory activity (page 46, lines 18-26). Thus, the specification discloses *in vivo* uses for a vector of the invention other than gene therapy uses and, it is submitted, it is well known that a composition need not be enabled for every embodiment encompassed within the claim. As such, it is respectfully requested that the rejection be removed for the above reasons.

Notwithstanding the above, claims 9 and 18 nevertheless have been amended to refer more specifically to "isolated" host cells, as suggested by the Examiner, in order to advance prosecution of the subject application. It is noted that the suggestion to amend the vector claims to refer to an "isolated" vector also was suggested. Applicants submit, however, that such an amendment should not be required because, 1) the form of the vector is not relevant with respect to enablement of a gene therapy procedure, and 2) the amendment would unduly limit the scope of protection to which the Applicants are entitled; it would be a simple matter to avoid infringement of "isolated vectors" by simply omitting a final purification step. As such, it is respectfully requested that the rejection be removed with respect to claims 6 to 8, 16 and 17.

In view of the amendment to claims 9 and 18, and for the reasons set forth above with respect to claims 6 to 8, 16 and 17, it is submitted that the skilled artisan would have known how to practice the claimed invention without undue experimentation. Accordingly, it is respectfully requested that the rejection of claims 6 to 9 and 16 to 18 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement be removed.

The rejection of claims 20 and 21 under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description is respectfully traversed.

With respect to claim 20, it is stated in the Office Action that the claimed oligonucleotides minimally hybridize to residue 2414, 2766, 3013 or 3786 of SEQ ID NO:1, and that the limitations of "wherein at least three nucleotides of said oligonucleotide hybridize to a nucleotide sequence 5' and contiguous to said nucleotide position, and wherein at least three nucleotides of said oligonucleotide hybridize to a nucleotide sequence 3' and contiguous to said nucleotide position" do not further define the sequence to which the oligonucleotide hybridizes because the claim refers only to "a nucleotide sequence" and not to specific residues of SEQ ID NO:1. Claim 20 has been amended to clarify that that oligonucleotide hybridizes to "a nucleotide sequence of SEQ ID NO:1" that is 5' and contiguous with and that is 3' and contiguous with a nucleotide position as recited.

It is submitted that amended claim 20 clearly indicates that hybridizing oligonucleotides of the invention encompass those oligonucleotides that can specifically hybridize to a nucleotide sequence of SEQ ID NO:1 that includes and spans a splice junction of the disclosed Mcl-1 gene. It is noted that such oligonucleotides are disclosed, for example, at page 38, lines 5-12, of the specification and, therefore, are adequately described by the subject application. Accordingly, it is respectfully requested that the rejection be removed with respect to claim 20.

With respect to claim 21, it is stated that there is no limitation in the claim that residues 2412-2414 be directly linked to residues 3678-3770 and, therefore, that the hybridizing oligonucleotide read on any AAG sequence in frame with a GAT sequence. Claim 21 has been amended to more clearly indicate that the recited residues are "operatively linked and contiguous to" each other. As disclosed in the subject application, such oligonucleotides, in which the recited residues, or their complements, are directly linked to each other, can hybridize specifically to a polynucleotide encoding a variant Mcl-1/ΔTM polypeptide, wherein the variant is generated by an alternative splicing event in which exon 1 is joined to exon 3 (see

page 39, lines 4-10). As such, it is submitted that the subject application adequately describes the subject matter of amended claim 21 and, therefore, respectfully requested that this ground of rejection be removed.

In summary, the claims have been amended to more clearly set forth the structural requirements of an oligonucleotide of the invention, i.e., that the oligonucleotide can hybridize to a nucleotide sequence comprising a splice junction of an Mcl-1 gene as disclosed in the specification. Accordingly, it is submitted that one skilled in the art, reading the claims in view of the specification, would have known that the Applicants were in possession of the claimed subject matter and, therefore, respectfully requested that the objection to the specification and corresponding rejection of claims 20 to 21 under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description be removed.

E. Prior Art Rejections

The rejection of claims 20 and 21 under 35 U.S.C. § 102(b) as allegedly anticipated by Kozopas et al., as evidenced by Accession No. L08246, is respectfully traversed. It is noted that the Office Action inadvertently refers to Acc. No. L08248.

It is stated in the Office Action that the claimed compositions are anticipated by the sequence in Acc. No. L08246 because, when given their broadest reasonable interpretation, claim 20 reads on a nucleotide sequence comprising a single nucleotide (e.g., nucleotide 2414 of SEQ ID NO:1), and claim 20 reads any nucleotide sequence containing AAG in frame with GAT. It is stated, for example, that nucleotides 1727 to 2414 of SEQ ID NO:1 are identical to residues 61-748 of Acc. No. L08246, and that nucleotides 2766 to 3013 of SEQ ID NO:1 are identical to nucleotides 749-996 of Acc. No. L08246.

As an initial matter, it is noted that Kozopas et al. do not teach or suggest oligonucleotide portions of the nucleotide sequence set forth as Acc. No. L08246. As such, it is submitted that the cited art is relevant only with respect to the full length Mcl-1 cDNA as set forth in Acc. No. L08246.

Amended claim 20 requires that a hybridizing oligonucleotide of the invention specifically hybridize to a nucleotide sequence of SEQ ID NO:1 comprising an Mcl-1 gene splice junction, including at least 3 nucleotides, as set forth in SEQ ID NO:1, on each side of a recited nucleotide (e.g., nucleotide 2414). As such, an oligonucleotide of claim 20 specifically hybridizes to a nucleotide sequence comprising exon sequences and intron of the Mcl-1 gene sequences (see Figure 1). Kozopas et al. (L08246) describe a full length Mcl-1 cDNA, which, as is known in the art, is generated from mRNA and consists only of "exon" sequences. It is submitted that the full length Mcl-1 cDNA would not specifically hybridize to a nucleotide sequence of SEQ ID NO:1 as defined in claim 20 and, therefore, that Kozopas et al. does not anticipate an oligonucleotide of the invention.

Even if it is considered for argument sake, that Kozopas et al. describe fragments of the cDNA of Acc. No. L08246, there is nothing in the reference that would teach or suggest to one skilled in the art to identify a potential fragment of the Mcl-1 cDNA that specifically hybridizes with a nucleotide sequence of SEQ ID NO:1 including a splice junction comprising one of the recited nucleotides (e.g., nucleotide 2414) and at least three nucleotides of an exon (e.g., nucleotides 2411-2413) and at least three nucleotides of an intron (e.g., nucleotides 2415-2417). As such, it is submitted that Kozopas et al. do not anticipate (or render obvious) the claimed oligonucleotides for this reason.

Further, even if the artisan was aware of the splice junction sites of the Mcl-1 cDNA, it is submitted that a fragment of the Mcl-1 cDNA (Acc. No. L08246) would not specifically hybridize with a nucleotide sequence of SEQ ID NO:1 as defined in claim 20. For example, the nucleotide sequence of SEQ ID NO:1 that includes residue 2414 and 3 residues on each side (i.e., residues 2411-2417) reads "caaggta" (see, also, Figure 1), thus defining, with respect to nucleotide 2414, a "minimal" target sequence for an oligonucleotide of the invention, which contain at least ten nucleotides. In contrast, a nucleotide sequence of Acc. No. L08246 that includes residue 748, which corresponds to nucleotide 2414 of SEQ ID NO:1, and 3 nucleotides on either side of residue 748, reads "caaggca" (see Exhibit A, sequence highlighted), which is different from the "caaggta" sequence of SEQ ID NO:1 (differences

indicated by underlining). A similar analysis of oligonucleotides of claim 20 that contain either of nucleotides 2766, 3013, or 3786 reveals that none of the "minimal" sequences is contained in L08246, a result that is not unexpected because L08246 provides a Mcl-1 cDNA molecule, whereas each of the claimed oligonucleotides hybridizes to a portion of the Mcl-1 gene that include exon sequences and intron sequences. As such, it is submitted that even if the cited reference teaches or suggests oligonucleotide fragments of Acc. No. L08246 that include exon sequences contiguous to a splice junction of the Mcl-1 gene, it is merely speculative as to whether such fragments would specifically hybridize to a nucleotide sequence of SEQ ID NO:1 as defined by claim 20 because such fragments would not contain an intron nucleotide sequence. Accordingly, it is submitted that the cited references cannot anticipate (or render obvious) the subject matter of claim 20.

Amended claim 21 requires that an oligonucleotide contain at least ten nucleotides that hybridize specifically to a nucleotide sequence of SEQ ID NO:1 that includes nucleotides 2412-2414 of SEQ ID NO:1 operatively linked and contiguous with nucleotides 3768-3770 of SEQ ID NO:1. As such, the claims define a "minimal" target sequence "aaggat" to which an oligonucleotide of the invention hybridizes specifically. For the reasons discussed above, it is submitted that Kozopas et al. do not anticipate the oligonucleotides of claim 21 because the reference only teaches a full length Mcl-1 cDNA, which, it is submitted, would not specifically hybridize with a nucleotide sequence of SEQ ID NO:1 as defined in claim 21.

Further, even if it is considered for argument sake that the reference describes fragments of the Mcl--1 cDNA (Acc. No. L08246), it is submitted that the reference would not anticipate (or render obvious) the claimed oligonucleotides because the Mcl-1 cDNA does not contain fragments that would hybridize specifically to a nucleotide sequence of SEQ ID NO:1 as defined by claim 21. More specifically, the smallest oligonucleotide of claim 21 contains 10 nucleotides, and hybridizes to a nucleotide sequence of SEQ ID NO:1 that includes nucleotides 2412-2414 linked to 3768-3770 (i.e., "aaggat"). As such, the oligonucleotide would need to include at least four additional nucleotides, which, with reference to SEQ ID

NO:1, can include nucleotides 2408-2411, 3771-3774, and various combinations (e.g., 2409-2411, 2412-2414, 3367-3370, and 3371). As such, the minimal sequences to which an oligonucleotide of claim 21 must hybridize include ttccaaggat, tccaaggatg, ccaaggatgg, and caaggatggg (see Figure 1, nucleotides 2409-2414 and 3768-3774); L08246 does not contain any of these sequences. As such, even if Kozopas et al. (and Acc. No. L08246) teach or suggest fragments of the Mcl-1 cDNA, it is submitted that the reference(s) does not teach or suggest fragments encompassed within claim 21. As such, it is respectfully requested that this ground of rejection be removed.

In summary, it is submitted that the cited references do not teach or suggest oligonucleotides encompassed within amended claim 20 and 21 because 1) the references only describe a full length Mcl-1 cDNA, which would not specifically hybridize to a nucleotide sequence of SEQ ID NO:1 as defined by claims 20 and 21; 2) even if it is considered that the references suggest fragments of the Mcl-1 cDNA, the references do not teach or suggest the positions of Mcl-1 gene splice junctions such that one of ordinary skill could identify fragments meeting the requirements of the claimed oligonucleotides; and 3) even if it is considered that the references further suggest such splice junctions, it is speculative as to whether fragments of the Mcl-1 cDNA would specifically hybridize to a nucleotide sequence of SEQ ID NO:1 as defined in the claims. Accordingly, it is respectfully requested that the rejection of claims 20 and 21 under 35 U.S.C. § 102(b) as anticipated by Kozopas et al., in view of Acc. No. L08246, be removed.

The rejection of claims 10, 14, 20 and 21 under 35 U.S.C. § 102(b) as allegedly anticipated by The New England Biolabs Catalog (1993-1994; page 91) is respectfully traversed.

It is stated that the random hexamers described in the cited catalog anticipate the claimed oligonucleotides because the claims do not require that the recited complementary oligonucleotides comprise at least ten nucleotides. As an initial matter, it is submitted that the

cited reference teaches a pool of random hexamers containing 4096 (4^6) different hexamers, one or more of which may have the characteristic of being able to selectively bind to a nucleotide sequence of SEQ ID NO:1 as defined within the claims. However, the reference does not specifically teach such a nucleotide sequence and, it is submitted, undue experimentation would have been required for one of ordinary skill to identify the hexamer(s) encompassed within the claimed invention, particularly absent knowledge of the Mcl-1 gene and intron/exon splice junctions of the Mcl-1 gene. It has long been recognized that a reference, to be anticipatory, must be enabling, thus placing the allegedly disclosed matter in the possession of the public (see., e.g., *Akzo N.V. v. U.S. ITC* 1 USPQ2d 1241 (Fed. Cir. 1986); *In re Spada* 15 USPQ2d 1655 (Fed. Cir. 1990)). It is submitted that a disclosure of random hexamers does not place an oligonucleotide of claim 20 or 21 in the possession of the public and, therefore, is respectfully requested that the rejection be removed for this reason.

Notwithstanding the above reason for removing the rejection, Applicants point out that claims 20 and 21 have been amended to more clearly indicate that a "polynucleotide" complementary to the recited oligonucleotides, which comprise at least ten nucleotides, also "comprise at least ten nucleotides". Since the cited reference describes hexamers, it cannot anticipate the claimed oligonucleotides, or the polynucleotides complementary thereto, which contain at least ten nucleotides. Accordingly, it is respectfully requested that the rejection of claims 10, 14, 20 and 21 under 35 U.S.C. § 102(b) be removed

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: October 23, 2003

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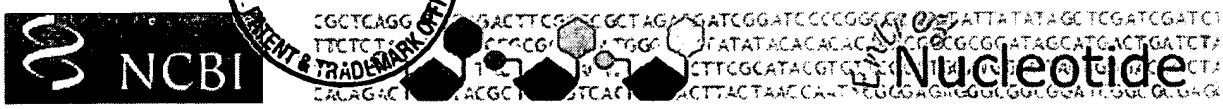
Enclosures: Exhibit A
Attachment A - Replacement page 70



☐ **1:** L08246. Human myeloid cel...[gi:307165] Links

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LOCUS       HUMMCL1X                3934 bp    mRNA    linear   PRI 26-JUL-1993
DEFINITION  Human myeloid cell differentiation protein (MCL1) mRNA.
ACCESSION   L08246
VERSION     L08246.1  GI:307165
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (bases 1 to 3934)
  AUTHORS   Kozopas,K.M., Yang,T., Buchan,H.L., Zhou,P. and Craig,R.W.
  TITLE     MCL1, a gene expressed in programmed myeloid cell differentiation,
            has sequence similarity to BCL2
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 90 (8), 3516-3520 (1993)
  MEDLINE   93234528
   PUBMED   7682708
COMMENT     Original source text: Homo sapiens early in the induction of
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      301 cccattggcg ccgaggtccc cgacgtcacc gcgacccccg cgaggctgct tttcttcgcg
      361 cccacccgcc gcgcggcgcc gcttgaggag atggaagccc cggccgctga cgccatcatg
      421 tcgcccgaag aggagctgga cgggtacgag ccggagcctc tcgggaagcg gccggctgtc
      481 ctgccgctgc tggagttggt cggggaatct ggtaataaca ccagtacgga cgggtcacta
      541 ccctcgacgc cgccgccagc agaggaggag gaggacgagt tgtaccggca gtcgctggag
      601 attatctctc ggtaccttcg ggagcaggcc accggcgcca aggacacaaa gccaatgggc
      661 aggtctgggg ccaccagcag gaaggcgctg gagaccttac gacgggttgg ggatggcgtg
      721 cagcgcaacc acgagacggt cttccaagac atgcttcgga aactggacat caaaaacgaa
      781 gacgatgtga aatcgttgtc tcgagtgatg atccatgttt tcagcgacgg cgtaacaaac
      841 tggggcagga ttgtgactct catttctttt ggtgcctttg tggctaaaca cttgaagacc
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     1021 gtagaggacc tagaaggtgg catcaggaat gtgctgctgg cttttgcagg tgttgctgga
     1081 gtaggagctg gtttggcata tctaataaga tagccttact gtaagtgcaa tagttgactt
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Exhibit A

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1141 ttaaccaacc accaccacca ccaaaaccag tttatgcagt tggactccaa gctgtaactt
1201 cctagagttg caccctagca acctagccag aaaagcaagt ggcaagagga ttatggctaa
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1861 ttacattagt ttttttcata ccctttttgaa ctttgcaact tccgtaatta ggaacctgtt
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1981 attgatgtgt aactgtatgc agactggttg tagtggaaca aatctgataa ctatgcaggt
2041 ttaaattttc ttatctgatt ttggtaagta ttccttagat aggttttctt tgaaaacctg
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3781 acaccttggt tctggttaaa cagctgtact tttgatagct gtgccaggaa gggttaggac
3841 caactacaaa ttaatgttgg ttgtcaaatg tagtgtgttt ccctaacttt ctgtttttcc
3901 tgagaaaaaa aaataaatct tttattcaaa taaa
//
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Table 1. Mcl-1 contains an intron downstream of the BH3 domain in a position conserved in pro-apoptotic Bax but not Bcl-2 or other anti-apoptotic family members, in addition th the conserved intron further downstream.

		Splice Donor	Splice Acceptor
Consensus:	20* CAG 21 A	gtagagt.....tttttttttttncag g ccccccccccc t	G A
Mcl-1 22 intron 1 23	AC CAC GAG ACG GCC TTC CAA G_{748} N H E T V F Q_{229}	gtaaggg.(351 bp).gcttttctttctcag	GC ATG CTT CTT CGG AAA CTG G_{230} M L R K L D
Mcl-1 24 intron 2 25	CTA GTT AAA CAA AGA GGC TGG_{996} L V K Q R G W_{312}	gtaagtt.(754 bp).ttttttgttttctag	GAT GGG TTT GTG GAG TTC D_{313} G F V E F
Bax 26 intron 3 27	AC ATG GAG CTG CAG AG N M E - - L Q	gtgtggg.....tcctctctcctgcag	G ATG ATT GCC GCC GTG GAC R M I A A V D
Bax 28 terminal 29 intron (intron 5)	GAT CAA GAC CAG GGT GGT TGG I Q D Q G G W	gtgagac.....ccctgtctctccagg	GAC GGC CTC CTC TCC TAC D G L L S Y
Bcl-2 30 terminal 31 intron	ATC CAG GAT AAC GGA GGC TGG I Q D N G G W	gtaggtg.....tgcag	GAT GCC TTT GTG GAA CTG D A F V E L

The positions of Mcl-1 introns 1 and 2 within the coding sequence are shown. Intron 1 lies just downstream of the BH3 domain and intron 2 lies within the BH2 domain [4]. The length of introns 1 and 2 is indicated in parentheses. An intron at a position similar to that of Mcl-1 intron 1 is present in the Bax gene (intron 3), but not in Bcl-2. An intron at the position of Mcl-1 intron 2 is a highly conserved feature of the Bcl-2 family. Thus, a terminal intron at a similar position is present in Bax (intron 5), as well as Bcl-2 and other family members. Dashes were inserted to optimize sequence alignment [4]. Subscripts indicate the numbering of the full length Mcl-1 cDNA and amino acid sequence (the latter in bold). * SEQ ID NO:.